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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/767,200	01/30/2004	Antonio Molinari	28317	5721

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EXAMINER	
GRUN, JAMES LESLIE	
ART UNIT	**PAPER NUMBER**
1641	

DATE MAILED: 10/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/767,200	MOLINARI ET AL.	
	Examiner	Art Unit	
	James L. Grun	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 07/903,797.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *01/30/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The preliminary amendment filed 30 January 2004 is acknowledged and has been entered. Claims 1-12 remain in the case.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention, and failing to adequately teach how to make and/or use the invention, i.e. failing to provide an enabling disclosure.

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, and which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factors present in the claims are the known sequences of the hirudins from *Hirudo medicinalis* and related proteins

from *Hirudo manillensis* and the suggestion that derivatives with anti-thrombin activity are also encompassed. In the specification (e.g. page 7), a further disclosure of a partial structure in the form of percent identity is provided. However, there is no identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement, which defines a genus of molecules by only their functional activity, does not provide an adequate written description of the genus. The court indicated that although applicants are not required to

disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of molecules falling within the scope of the claimed genus.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115). However, in view of the guidance in the instant specification only to SEQ ID NOs: 1-5, which function for anti-thrombin activity as intended by applicant, the amount of experimentation required to determine functional structures or modifications for other usable species would also be undue. Not knowing, absent further experimentation, which modifications function and which do not, leads to one having no predictability or expectation of success for the function of any given modification. Such random experimentation to identify, at a later time, what structure or fragment or modification is or is not functional and is embraced by applicant's claims is undue experimentation. Note that an enabling disclosure for the preparation and use of only a few analogs of a product does not enable all possible analogs where the characteristics of the analogs are unpredictable. See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.* (18 USPQ 2d 1027 (CAFC 1991)).

Therefore, only isolated polypeptides comprising the amino acid sequences set forth in SEQ ID NOs: 1-5, but not the full breadth of the claims, meet the written description and enablement provisions of 35 U.S.C. §112, first paragraph.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1-12, the recitation of "hirudin-like protein" is vague and indefinite with regard to what is encompassed within the metes and bounds of the claim, because it is not clear how "like" hirudin the "hirudin-like protein" needs to be.

Claims 2-4 should recite --The-- method for proper reference to the previously recited claim components.

Claims 6-8 should recite --The-- immunogen for proper reference to the previously recited claim components.

Claims 10 and 11 should recite --The-- method for proper reference to the previously recited claim components.

Claim 12 should recite --the-- immunogen for proper reference to the previously recited claim components. Method claims should recite positive, active steps, and "using" is not a proper method step. Ex parte Erlich (3 USPQ2d 1011 (BPAI 1987)).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 3-12 are rejected under 35 U.S.C. § 102(b) as being anticipated by Schlaeppi (Thromb. Res. 62: 459, 01 June 1991; hereafter TR) in light of Schlaeppi et al. (EP 0,380,443; hereafter EP).

Schlaeppi (TR) teaches that hirudin is poorly immunogenic in mice (e.g. page 460). The reference teaches making an immunogen comprising conjugates (i.e. random polymers) of recombinant hirudin HV1 with keyhole limpet hemocyanin carrier protein. It is noted by the examiner that the invention as instantly claimed does not exclude the presence of additional components such as the carrier protein. Moreover, the method of Schlaeppi (TR), which omitted an optional step of protecting the hirudin amino groups, inherently resulted in conjugates (i.e. polymers) of cross-linked (i.e. polymerized) hirudins in the immunogen composition of the reference, because in light of Schlaeppi et al. (EP), omission of this step allows such cross-linking to occur. It cannot be determined from the reference disclosure if cross-linked hirudin polymers were present unconjugated as well as conjugated to the carrier protein in the immunogen composition. Antibodies to the immunogen were elicited by immunization. Elicited antibodies were shown to bind free hirudin in solution and were used in immunoassays for determination of hirudin/thrombin complexes, as an additional assay to that known to the prior art which functioned, due to the specificity of the antibodies used, for determination of free hirudin only (e.g. page 460).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-12 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Schlaeppi (TR) taken with Schlaeppi et al. (EP).

The teachings of Schlaeppi (TR) are as set forth above and differ from the invention as instantly disclosed and/or claimed by conjugating (i.e. polymerizing) hirudin via the carbodiimide method rather than via glutaraldehyde and in exemplifying immunoassays for thrombin/hirudin complexes rather than for free or total hirudin.

Schlaeppi et al. (EP) teach that hirudin is a weak immunogen and that numerous methods are available for conjugating proteins for use as immunogens, including glutaraldehyde or carbodiimide treatment (page 5, lines 25-45; pages 11-12). Schlaeppi et al. (EP) further teach immunoassays for the quantitative determination of free hirudin using both monoclonal antibodies (pages 22-24) and polyclonal antibodies (pages 23-24), wherein anti-hirudin antibody is immobilized to a solid phase in order to capture the antigen.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have substituted glutaraldehyde for carbodiimide treatment in Schlaeppi (TR) because Schlaeppi et al. (EP) specifically teach such a substitution as a routine and conventional alternative for hirudin immunogen preparation. It would have been further obvious to have assayed for total and/or free hirudin in a sample in Schlaeppi (TR) using anti-hirudin antibodies, as taught by either or both of Schlaeppi (TR) or Schlaeppi et al. (EP), immobilized to a solid phase, as taught by Schlaeppi et al. (EP), which during the assay washing steps effectively isolate hirudin, because one would have reasonably expected the sandwich assay for hirudin known to the prior art to function for isolation and determination of free and/or total hirudin, depending upon the specificities of the selected immobilized capture antibodies and labeling antibodies for uncomplexed and/or thrombin-complexed hirudin, and one would have had obvious motivation to determine total hirudin in a sample by determination of total and/or free hirudin in addition to the determination of the protein bound to thrombin as implicitly suggested by either Schlaeppi (TR) or Schlaeppi et al. (EP).

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 1-10 and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Spinner et al. (J. Immunological Meth. 87: 79, 1986), in view of Spinner et al. (Thromb. Res. 51 : 617, 1988), Bichler et al. (Thromb. Res. 61 : 39, 1991), and Reichlin et al. (J. Biol. Chem. 245: 947, 1970).

Spinner et al. (1986) teach that a preparation apparently comprising unconjugated hirudin is weakly immunogenic after emulsification in complete Freund's adjuvant and elicits antibodies only in some animals (page 80, column 1). The antibodies were used in competitive immunoassays for hirudin determinations. However, Spinner et al. did not attempt to enhance the poor immunogenicity of hirudin (page 79, column 2) by, as in the instant claims, chemical conjugation reactions.

Spinner et al. (1988) teach that the antigen preparation used in this reference, and implicitly in Spinner et al. (1986), contained a mixture of hirudin isoforms. Antibodies specific for hirudin were elicited in rabbits and sheep and were used in sandwich immunoassays for hirudin determinations.

Bichler et al. teach that hirudin is a protein with very low immunogenic potential and suggest that this may be the result of its low molecular mass (M_r = 7,045 Da) (see pages 48-49).

Reichlin et al. provides evidence of the notoriously old and well-known technique of glutaraldehyde cross-linking/aggregation/polymerization for enhancement of weak immunogenicity of small proteins as an alternative to conjugation with bovine gamma-globulin or the emulsification of polypeptide monomers in Freund's adjuvant (see e.g. pages 951-952). The reference specifically exemplifies cytochrome c polymers/aggregates, but teaches that cytochrome c behaves similarly to other protein antigens (suggesting the general applicability of the method) in the "remarkable" enhancement of immunogenicity upon polymerization (see e.g. page 953), related perhaps to phagocytosis or to retardation of the renal excretion of the protein or to reduction in charge density.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have applied the notoriously old and well known teachings of Reichlin et al., i.e. the use of the aggregation of small proteins, including with the notoriously old and well known aggregation via glutaraldehyde, for the purpose of enhancing immunogenicity, to the preparation of an immunogen comprising hirudin for the elicitation of anti-hirudin antibodies for use in immunoassays as in Spinner et al. (1986 or 1988) because hirudin is of unquestioned clinical interest and was known to be immunogenic, but poorly immunogenic by itself (Spinner et al. (1986) or Bichler et al.), hirudin may have had very low immunogenic potential as a result of its low molecular mass (Bichler et al.), and one of ordinary skill in the art would have had an extremely reasonable expectation of increasing the immunogenicity of the protein and eliciting antibodies with the protein by notoriously old and well known methods such as by the aggregation of the protein by conventional means such as glutaraldehyde cross-linking as taught in Reichlin et al. as an alternative to mere emulsification of the small protein in Freund's adjuvant as done in Spinner et al. because of the general applicability of the method suggested in Reichlin et al. It would have been further obvious to have elicited antibodies to a plurality of isoforms of hirudin because Spinner et al. (1988) teach that available preparations of the protein contain mixtures of isoforms.

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,719,975 B1. Although the conflicting claims are not identical, they are not patentable distinct from each other because the species and subgenus claims of the patent make obvious the species and genus claims of the instant application that recite immunogenic compositions, methods of making, or methods of use comprising generically polymerizing the same hirudin species.

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Schlaeppi et al. (U.S. Pat. No. 5,272,059) teach the methods and antibodies of Schlaeppi et al. (EP).

Maschler et al. (U.S. Pat. No. 5,114,922) teach affinity chromatography with anti-polypeptide antibodies or thrombin for the isolation of an antithrombic polypeptide from leeches (Column 3, lines 32-39). However, Maschler et al. teach the isolation of hirullins rather than hirudin.

Schlaeppi et al. (Eur. J. Biochem. 188: 463, 1990) teach that the C-terminal amino acid residues of hirudin are necessary for the inhibition of thrombin (page 463, col 2). The reference teaches the conjugation of HV1 hirudin or hirudin peptide fragments to carrier proteins for use as immunogens (page 464, col 1). One of the immunogen preparations was made by Schlaeppi et al. by treating mixtures of recombinant HV1 hirudin C-terminal peptide fragments and various carrier proteins with glutaraldehyde. The resultant conjugated mixtures were used as immunogens for the elicitation of polyclonal and monoclonal anti-hirudin antibodies (page 464). All the polyclonal and monoclonal anti-hirudin antibodies elicited by the methods of the reference bound native recombinant hirudin in solution (page 465, Col 1; page 466, Table 1).

Maurer et al. (Meth. Enzymol. 70: 49, 1980) teach that the method by which a protein or polypeptide immunogen is presented to a host can influence the ability of that immunogen preparation to elicit a response, i.e. by employing the correct "carrier" and conjugation procedure for a protein or polypeptide, an immune response to almost any macromolecule (even those believed to be nonimmunogenic) can be elicited (page 50). Further, in general, the greater the

molecular weight and the more complex the structure of the macromolecule, the greater the immune response one would reasonably expect to obtain (page 50). For example, the state of aggregation of a protein is involved in immunogenicity and various proteins, e.g. bovine γ-globulin, human γ-globulin, or bovine serum albumin, have been shown to be immunogenic, or more immunogenic, only when aggregated (pages 53 and 59) (i.e., when presented in a more complex structure having a higher molecular weight). Thus, the reference teaches that it is advisable to aggregate a protein artificially in order to enhance the immunogenicity of the protein (page 59). Maurer et al also teach typical protocols for both polyclonal and monoclonal antibody production (pages 64-67).

Man et al. (J. Immunological Meth. 125: 251, 1989) teach that it is notoriously old and well-known in the art that aggregated (i.e. polymerized) forms of monomeric proteins are more immunogenic (e.g. page 252). The reference teaches incubation with glutaraldehyde, which is known to cross-link (i.e. polymerize) proteins via amino groups, for deliberate chemical aggregation of smaller (prior art) (like hirudin or cytochrome c) and larger (like creatine kinase) protein monomers in order to produce an immunogen which is more immunogenic than the monomeric protein. Although the reference suggests that the use of glutaraldehyde for larger globular proteins may not be universally applicable, this is only because a single form of creatine kinase, that from human brain, could not be efficiently aggregated therewith to produce an aggregated immunogen. A presence or lack of aggregation/polymerization is clearly the relevant consideration in this passage. The teaching of an inability to form an aggregate with a particular protein does not, in any way, teach away from that which was notoriously old and well known in the art regarding the increased immunogenicity of aggregated smaller (prior art) and, as taught in

the reference, aggregated larger protein monomers. Moreover, teaching against the universal applicability of a method is not seen as teaching against one having had a reasonable expectation of success because absolute predictability, i.e. universality, is not that which is required for a determination of obviousness.

Sadahiro et al. (Japan. J. Med. Sci. Biol. 37: 225, 1984) teach that the extent of polymerization of a snake venom toxoid paralled its immunogenicity (see e.g. page 230).

Shigeta et al. (Jpn. J. Allergol. 39 : 313, 1990) teach that polymerization of a small (MW 9,980) protein allergen from sea squirt using glutaraldehyde markedly improved the low efficacy of the antigen in hyposensitization therapy. The increased therapeutic efficacy of the polymerized antigens could be ascribed to their increased molecular weight and enhanced immunogenicity (see e.g. pages 319-320).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, SPE, can be contacted at (571) 272-0823.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

James L. Grun, Ph.D.
September 26, 2005

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09/29/05